

REMARKS

Claims 8, 19, and 20 are cancelled without prejudice. No claims have been added or amended. Claims 1-7, 9-18, and 21-25 are pending.

Applicants wish to thank the Examiner and her supervisor, Brandon Fetterolf, for the courtesy of a telephonic interview on March 19, 2009 with Applicants' representative Brian Bean. During the interview, the nature of the invention was discussed as well as the merits of the pending rejections under 35 U.S.C. § 103(a). Applicants' representative requested that the Examiner provide some motivation to combine the cited references, and suggested that the combination of cited references would not produce the claimed invention. No agreement was reached with respect to the pending claims.

Rejections Under 35 U.S.C. § 103 (a)

Claims 1-4, 6-18 and 21-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,444,234 to Kirby et al. ("Kirby"), in view of WO 02/40033 to Tocovite Party Ltd. ("Tocovite"), and further in view of U.S. Patent Pub. 2003/0157326 to Vaghefi et al. ("Vaghefi"). Office action at 3.

Kirby discloses pharmaceutical compositions for the transdermal administration of a medicament, or other active agent, by topical application of the composition to the skin of humans. Abstract. The pharmaceutical compositions are formulated to provide for very rapid uptake of the medicament and transmigration into and through the skin to either fatty tissues or the vascular system, while minimizing irritation to the skin and/or immunological response. Abstract. The pharmaceutical compositions are based on a transdermal delivery system (TDS) wherein the medicament is modified to form a true solution in a complex formed from particular solvents and solvent and solute modifiers in combination with skin stabilizers. Abstract.

Tocovite discloses an emulsion composition comprising a particular equimolar amount of a mono-electron transfer agent phosphate derivative (e.g., mono-tocopheryl phosphate), a di-electron transfer agent phosphate derivative (e.g., di-tocopheryl phosphate), and a suitable carrier. Abstract. The phosphorylated electron transfer agents may be complexed with a complexing agent selected from amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids. Tocovite at 4.

Vaghefi teaches pharmaceutical compositions comprising microspheres with a water insoluble organic matrix in an interior region, throughout which are dispersed a plurality of microcapsules containing hydrophobic bioactive compounds. Abstract. The microcapsules located in the interior of the microspheres are coated with pharmaceutically-acceptable, charged

(hydropilic) materials, thereby providing facilitating the transport of the hydrophobic bioreactive compounds. See Abstract, paragraphs [0014] to [0019].

Applicants respectfully submit that a *prima facie* case of obviousness has not been established for the reasons set forth below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that one of skill in the art would not have been motivated at the time of the invention to combine Kirby, Tocovite, and Vaghefi for the reasons provided below. As the Federal Circuit recently clarified, when it comes to compositions, the question remains "whether, at the time of the invention, a person having ordinary skill in the art would have had reason to attempt to make the composition . . . and a reasonable expectation of success in doing so." Procter & Gamble v. Teva, No. 2008-1404 at 6 (Fed. Cir. 2009). Applicants note that the Examiner has relied on a combination of three references to reject the claims as being obvious. As such, failure to provide motivation to combine even two of the three references results in a failure to establish a *prima facie* case of obviousness. As set forth below, not only would one skilled in the art not be motivated to combine Kirby and Tocovite, but additionally one skilled in the art would simply dismiss Vaghefi in light of Kirby and Tocovite.

Applicants submit herewith the West Declaration, and note that the declarant, Dr. Simon Michael West, is also the sole inventor of Tocovite and, therefore, is uniquely situated to attest to what one of skill in the art would or would not have been motivated to do, particularly, in light of his Tocovite patent. Dr. West's comments on the development surrounding Tocovite, as well as his opinion regarding the motivation Tocovite might or might not provide are found in paragraphs 6-8 of the West Declaration, and have not been recited herein for the sake of brevity. These portions of the West Declaration, however, are very useful in understanding the context of Tocovite and how it relates with the other cited references.

With that said, one of skill in the art would not be motivated to combine Kirby and Tocovite for the following reasons. As stated in the West Declaration, one of skill in the art

would not have been motivated to utilize tocopherol phosphate with alkaloids because phosphate derivatives were considered unsuited for inclusion in alkaloid formulations:

The formulations of Kirby may apply the same general chemistry of association, in that a weak complex is formed between the active agent and its other components. However, Kirby follows the practice of transdermal transport based on the careful studies of the migration of a wide variety of molecules through the skin. This theory excludes sulfate and phosphate derivatives because they were not considered to efficiently transfer through the skin and thus would not have been considered appropriate or suitable for such formulations.

West Declaration at paragraph 10.

Dr. West further attests that "Tocovite would not have suggested modifying the formulations of Kirby to arrive at the claimed invention. In particular, one of skill in the art would not have been motivated to 1) phosphorylate the electron transfer agents in the solvent modifiers of Kirby, 2) use water as a solvent, rather than the ethanol/propylene glycol solvent of Kirby, [and] 3) remove the forskolin of Kirby." West Declaration at paragraph 12. Accordingly, because one of skill in the art would not be motivated to combine these two references, a *prima facie* case of obviousness has not been established, and the obviousness rejection cannot stand.

Furthermore, the West Declaration provides reasons why one of skill in the art would simply dismiss Vaghefi, in light of Tocovite and Kirby, thereby providing an additional reason why a *prima facie* case of obviousness has not been established. Particularly, Dr. West states the following:

In my opinion, those skilled in the art, considering Vaghefi in light of Tocovite, Kirby, or both, would simply dismiss Vaghefi because Vaghefi requires elaborate microsphere structures to assure that hydrophobic compounds can be transported across the dermal boundary. Vaghefi at [0014] to [0017]. The microspheres of Vaghefi are prepared by a process comprising spraying, into a chilling zone, a flowable dispersion of bioactive micron sized organic particles containing charged organic moieties in a water insoluble fluid matrix, under conditions that form droplets of said dispersion, and maintaining the fluidity of, and charge on, said droplets for a time sufficient to distribute homogeneously said particles within said droplets, and solidifying said droplets into said microspheres. Vaghefi at [0015]. The particles are then incorporated in pharmaceutical compositions. Vaghefi at [0016]. Therefore, contrary to the Examiner's assertion that Vaghefi stands for and would provide motivation for using tocopherol phosphate as a bio enhancer, it is my opinion that one skilled in the art would instead glean from Vaghefi an elaborate system that is much different from, and not compatible with, Tocovite or Kirby. As such, Vaghefi would be readily dismissed.

West Declaration at paragraph 15.

Accordingly, the ready dismissal of Vaghefi provides an additional reason why a *prima facie* case of obviousness has not been established.

In summary, the Examiner has based the obviousness rejection on the combination of not two, but rather, three references. Applicants have demonstrated that one of skill in the art would not be motivated to combine Kirby and Tocovite, which alone is sufficient to counter the obviousness rejection. Moreover, Applicants have provided additional reasons why one of skill in the art would simply dismiss Vaghefi, in light of Kirby and Tocovite. Accordingly, one of skill in the art would not have been motivated at the time of the invention to combine Kirby, Tocovite, and Vaghefi. As such, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Even assuming, *arguendo*, that one of skill in the art would have been motivated to combine the references, the combination would not teach or suggest all of the claimed elements for the reasons set forth below. Specifically, the combination would not produce a composition that is as effective as the formulations of the claimed invention, as is evidenced by Dr. West's statement in paragraph 13:

[I]n my opinion, phosphorylating Kirby's solvent modifiers, e.g., lemon oil (or/and d-limonene), Vitamin E, Pro-Vitamin 8, D-panthenol and methylsulfonylmethane (MSM), (Kirby col. 11, Ins. 11-14) would not achieve the efficacy of the claimed alkaloid formulations. This is because the Stock Delivery System of Kirby is highly unsuitable for use with sulfate or phosphate derivatives of hydrophobic substrates.

West Declaration at paragraph 13.

In view of the foregoing and the West Declaration, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to independent claim 1. Accordingly, independent claim 1 is allowable. Reconsideration and allowance of claim 1 are respectfully requested.

Independent claim 21 also stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Kirby, Tocovite, and Vaghefi. Office action at 3. Applicants submit, for the same and similar reasons as set forth above with respect to claim 1, that the examiner has not met her burden to make a *prima facie* case of obviousness for claim 21. Accordingly, independent claim 21 is allowable. Reconsideration and allowance of claim 21 are respectfully requested.

Claims 2-7, 9-18, and 23-25 depend from allowable independent claim 1, and are therefore allowable. Claim 22 depends from allowable independent claim 21, and is therefore allowable. Claims 2-7, 9-18 and 21-25 may also contain additional patentable subject matter for

reasons not stated herein. Reconsideration and allowance of claims 2-7, 9-18 and 21-25 are respectfully requested.

CONCLUSION

In view of the foregoing, reconsideration and allowance of the application are respectfully requested. If a conference call would be useful in resolving issues arising from the filing of this communication, please contact the undersigned at the below-noted number.

Respectfully submitted,

/gregory j. hartwig/

Gregory J. Hartwig
Reg. No. 46,761

File No. 024944-9015 US00
Michael Best & Friedrich LLP
100 East Wisconsin Avenue
Suite 3300
Milwaukee, Wisconsin 53202-4108
414.271.6560